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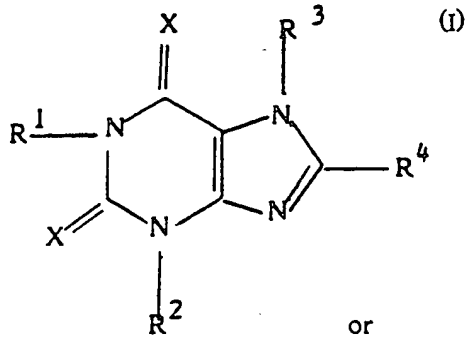
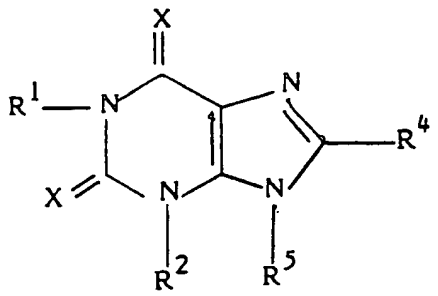
(54) Title: XANTHINE DERIVATIVE PEST CONTROL AGENTS



(I)

or



(II)

(57) Abstract

The use of xanthine derivatives having general formula (I) or (II) as pesticidal and pestistatic agents, as well as pesticidal and pestistatic compositions containing same.

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## DESCRIPTION

TITLE OF THE INVENTION:

# XANTHINE DERIVATIVE PEST CONTROL AGENTS

## TECHNICAL FIELD

The present invention is directed to a method for controlling a pest comprising bringing into contact with the pest a pest-controlling amount of a compound from the group comprising derivatives of xanthine.

## BACKGROUND ART

Despite the recent development and great promise of such advanced pest-controlling compositions as chemical sterilants, pheromones or ecologically-based insect control strategies, it is doubtless that, at present, the use of chemical pesticides still plays a predominant role. The use of insecticides often represents the difference between profitable crop production for farmers and no marketable crop at all, and the value of insecticides in controlling human and animal diseases has been dramatic.

Therefore, in parallel to the aforementioned newer technologies for pest control, there has been active research and investigation into the detailed bio-chemical modes of action of existing known chemical pesticides. Thus, for example, Nathanson, et al., Molecular Pharmacology, 20: 68-75 (1981), presented

evidence indicating that the formamidine pesticides chlordimeform (CDM) and N-demethylchlordimeform (DCDM) may affect octopaminergic neurotransmission. CDM and DCDM have been reported to mimic the effects of octopamine in stimulating light emission in the firefly lantern (Hollingworth, R. M., et al., Science, 208: 74-76 (1982)) and in effecting nerve-evoked muscle responses in the locust leg (Evans, P. D., Nature, 287: 60-62 (1980)). Nathanson, et al., supra, found that DCDM, which is the probable in vivo metabolite of CDM is about six-fold more potent than octopamine itself as a partial agonist of light organ octopamine-stimulated adenylate cyclase. Stimulation by the formamidines resulted in increased formation of the intracellular messenger, cyclic AMP (cAMP). This stimulation was blocked by cyproheptadine, clozapine, fluphenazine and phentolamine compounds, also known to block the octopamine receptor. Nathanson, et al., concluded that DCDM is the most potent octopaminergic compound described.

Similar results were observed by Hollingworth, et al. (reported in the Scientific Papers of the Institute of Organic and Physical Chemistry of Wroclaw Technical University, Number 22, Conference 7 (1980)). These authors demonstrated that certain formamidines act on octopamine receptors to induce the synthesis of cyclic AMP, and that this response is blocked by both phentolamine and cyproheptadine, which are known to act as octopaminergic antagonists in insects. The authors also suggested that these formamidines are potent stimulators of the octopamine sensitive adenylate cyclases in the thoraxic ganglia of Periplaneta

americana, and in the ventral nerve cord and fat body of M. sexta. The authors suggest that the stimulation of octopamine receptors underlies a number of toxic responses seen with formamidines on insects.

It should be noted that the presence of an insect adenylate cyclase enzyme which is sensitive to naturally occurring D(-)octopamine as a "neuro transmitter" has been known for some time (Nathanson, et al., Science 180: 308-310 (1973) (cockroach); Nathanson, Ibid, 203: 65-68 (1979) (firefly); Evans, J., Neurochemistry, 30: 1015-1022 (1978) (cockroach)).

The study of cyclic AMP as a "second messenger" has led to the accepted model that a hormone or neuro transmitter binds at a cell-membrane bound receptor, which activates adenylate cyclase to a form capable of converting ATP in the cytoplasm of the cell into cAMP. cAMP then relays the signal brought by the hormone or neuro transmitter from the membrane to the interior of the cell. Agonists of the hormone or neuro transmitter are, by definition, capable of eliciting the same response (see, for example, Nathanson and Greengard, Scientific American, 237: 108-119 (1977)). Among other actions, cAMP stimulates the conversion of inactive phosphorylase b into phosphorylase a, a reaction catalysed by phosphorylase kinase. This reaction is, in turn, catalysed by an enzyme, now called protein kinase, which occurs in an inactive and active form. Its active form catalyses the phosphorylation of inactive phosphorylase kinase by ATP to yield the active phosphorylated form by a reaction in which ATP is the phosphate-group donor.

Protein kinase, the key enzyme in linking cAMP to

the phosphorylase system and to other cyclic AMP-regulated processes, is an allosteric enzyme, that is, an enzyme whose reactivity with another molecule is altered by combination with a third molecule that is not a substrate. Its inactive form contains two types of subunits, a catalytic (C) subunit and a regulatory (R) subunit which inhibits the catalytic subunit. cAMP is the allosteric modulator of protein kinase, binding to a specific site on the regulatory subunit and causing the inactive CR complex to dissociate, yielding R-cAMP complex, and the free C subunit, which is now catalytically active. Thus, cAMP removes the inhibition of enzyme activity that is imposed by the binding of the regulatory subunit (Lehninger, Biochemistry, Second Edition, pages 812-813). The enzyme responsible for the destruction of cAMP is phosphodiesterase, which catalyzes the hydrolytic reaction as follows:

$$cAMP + H_2O \xrightarrow{\text{phosphodiesterase}} \text{adenosine 5'-phosphate.}$$

It is known that phosphodiesterase activity is inhibited by caffeine and theophylline, alkaloids present in small amounts in coffee and tea. Both caffeine and theophylline have long been known to prolong or intensify the activity of epinephrine, presumably due to increased persistence of cAMP in cells stimulated by epinephrine.

Rojakovick, A. S., et al., Pesticide Biochemistry and Physiology, 6: 10-19 (1976), explored the interaction between insecticidal activity and cAMP as a secondary messenger, surveying the direct effects of a

variety of different types of insecticides upon the activities of adenylate cyclase and phosphodiesterase. The survey of the direct effects of TEPP, methylparaoxon, DDT, Dieldrin, Aldicarb, Dimetilan, Rotenone, Allethrin, and Oxythioquinox upon cockroach brain adenylate cyclase in vitro led the authors to the conclusion that the compounds have essentially no direct effects on adenylate cyclase in vitro. The same nine insecticides were also evaluated for their effect upon cockroach brain phosphodiesterase in vitro. Certain of the compounds showed a general relationship of increasing inhibition with increasing concentration of insecticide, while DDT and Dieldrin appeared to be activators of phosphodiesterase. Oxythioquinox proved to be the most potent inhibitor of cockroach brain phosphodiesterase, giving over 80% inhibition. By comparison, using identical assay techniques, 1,000-fold greater concentrations of aminophylline and theophylline, the most widely used phosphodiesterase inhibitors in adenylate cyclase assays, inhibited 83.2 and 73.8%, respectively. The authors concluded that, while Oxythioquinox and other quinoxoline dithiol derivatives were demonstrated to be potent in vitro inhibitors of phosphodiesterases, no direct relationship of this activity to their mode of toxic action could be determined. Finally, the authors concluded that the broad distribution of phosphodiesterases in the animal kingdom makes it unlikely that phosphodiesterase inhibition is a direct cause of the selective acaricidal activity of the compounds.

Calva, United States Patent 2,362,614, describes fluorine-containing insecticides. Disclosed are the

hydrofluoric acid addition compounds of ammonia-substituted compounds giving rise to primary, secondary or tertiary amines and polyamines. Insecticidal activity is described as derived from the direct combination of the fluorine-nitrogen link. Caffeine is included in the patent disclosure among the "alkylamines with or without substituent groups."

French Patent 2,138,186 to Aries discloses insecticidal compositions of urinylphosphate esters which are stabilized by purine derivatives. Included among the purine derivatives are purines substituted in the 2, 4 and 8 positions. No insecticidal activity, however, is attributed to the purine compounds, the compounds performing the function of stabilizing the active phosphorus compounds.

Rizvi, S. J. H., et al., Indian Journal of Experimental Biology, 18: 777-8 (1980), explored the herbicidal activity of ethanolic extracts of leaves and seeds of 49 different plants. The seed extract of Coffea arabica proved most potent. Fractionation of the extract of Coffea arabica in different organic solvents produced a variety of fractions, all of which were tested for the desired activity. The chloroform fraction completely inhibited the seed germination of the test weed at 5,000 ppm. The authors suggested Coffea arabica as a possible source of natural herbicide. The same authors, in Agra. Biol. Chem., 45 (5): 1255-1256 (1981), identified the active weedicidal ingredient as 1,3,7-trimethylxanthine (caffeine). No insecticidal activity for caffeine, however, was disclosed. Rizvi, S. J. H., et al., Journal of Applied Entomology, Volume 90, Number 4, pages 378-381 (1980),

studied the 1,3,7-trimethylxanthine isolate of Coffea arabica and found it to be effective as a chemosterilant for Callosobrucaus chinensis, causing nearly 100% sterility at a concentration of 1.5%. No suggestion of utility as a pesticidal agent was disclosed.

Given the continuous need for increased selectivity and effectiveness in pest control agents, it became desirable that pesticidal and pestistatic agents from naturally occurring products be developed. Although certain fluorinated amines, including fluorinated caffeine, have been suggested as pesticides (Calva, supra), other xanthine derivatives unsubstituted in the 1, 3, and 7 position (the hypoxyxanthines of Aries, supra) have been suggested as stabilizers for phosphate insecticides, and caffeine has been suggested as a chemisterilant (Rizvi et al., supra), the pesticidal and pestistatic action of xanthine derivatives has not been known prior to this invention.

## DISCLOSURE OF THE INVENTION

The xanthine derivatives, including caffeine and theophylline, are found in berries, seeds, and leaves of a number of species, including tea, coffee, cocoa and cola. Although methylxanthines are one of the most frequently used stimulants employed by the human population, their natural function in plants was not known up to the present. It is known, however, that to discourage insect feeding, many plants have evolved endogenous chemical defenses, ranging from specific toxins and substances with pheromone-like activity to less specific bitter-tasting aversive substances.

Based on observations by this inventor and others that the mode of action of certain formamidine pesticides was through their octopaminergic agonist activity on octopamine receptors present in the pest, and that these pest control agents were acting through generation of cAMP as a "second messenger," the inventor then observed that the effectiveness of octopaminergic agonist pest control agents could be greatly enhanced when the quantity and half-life of generated cAMP was augmented by inhibiting insect phosphodiesterase enzymes, which are capable of hydrolyzing cAMP. This observation, coupled with the known phosphodiesterase-inhibiting activity of the methylxanthines, led to the discovery of the invention embodied in applicant's commonly assigned co-pending United States Patent Application Serial Number 605,845, filed 1 May 1984, incorporated by reference herein.

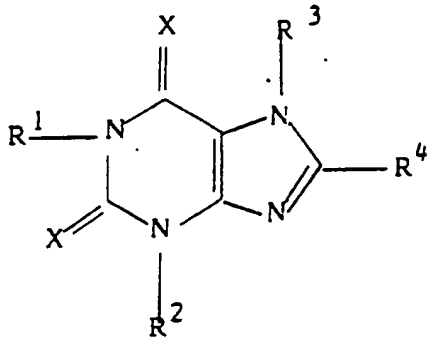
Recognizing the critical role that the phosphodiesterase inhibitors played in the enhancement of octopaminergic agonist pest control agents, the present inventor then began to explore the possibility of the use of certain phosphodiesterase inhibitors alone.

Initially, coffee and tea were investigated for pestistatic or pesticidal activity. The results of these experiments, reported below at Example 1, suggested that pesticidal and pestistatic activity existed for the coffee or tea.

To investigate the possible contribution of endogenous xanthine derivatives to the pesticidal activity described above, the action of purified

xanthine derivatives on insects, including Manduca larvae was examined. The results of one such experiment are reported below at Example 2, as well as the method of investigation. Based on the results of Example 2, it appeared that endogenous xanthine derivatives had pesticidal activity.

Endowed with this knowledge, the inventor then set out to explore the pesticidal and pestistatic activities of various xanthine derivatives, leading to the present invention. Thus, this invention comprises a method of pest control comprising bringing into contact with said pest a pest-controlling amount of an agent consisting essentially of a compound having the general formula (I) or (II):



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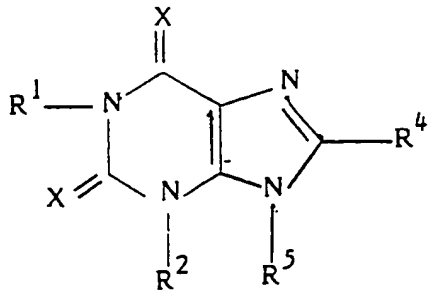


(II)

wherein:

X is oxygen or sulfur;

$R^1$, $R^2$, $R^3$, $R^4$ and $R^5$ are selected from hydrogen; aliphatic and cycloaliphatic hydrocarbons having 1-8 carbon atoms; substituted aliphatic and cycloaliphatic hydrocarbons substituted with 1-3 halogen atoms, lower alkyl ($C_1$-$C_4$), or hydroxy; alkoxy having 1-6 carbon atoms; aromatic; halo, hydroxy, or lower alkyl-substituted aromatic; phenoxy; substituted phenoxy; and the like, and acid addition salts of the above, where at least one of $R^1$, $R^2$, $R^3$, or $R^5$ is other than hydrogen.

Preferably, said agent is further defined by having a $V_{max}$ of more than 50%, where $V_{max}$ is expressed as the inhibition of feeding at the highest dose used, usually a 3% spray solution, and an $EC_{50}$ of less than 3% (gm/100 ml), $EC_{50}$ being the spray concentration required to cause 50% inhibition of feeding, as calculated from dose-response curves. The most preferred compounds have a $K_i$ of not more than 0.1, where $K_i$ is defined as the concentration in millimoles/liter of the xanthine derivative required to produce a 50% in vitro inhibition of the phosphodiesterase activity in tobacco hornworm nerve cord, using the conditions described.

## DESCRIPTION OF THE FIGURES

Figure 1A shows the effect on tobacco hornworm body weight of powdered coffee beans or caffeine incorporated into artificial media.

Figure 1B shows the dose-dependent antifeeding effect of caffeine.

Figure 1C is a graph quantitating the antifeeding effect of caffeine and other xanthine derivatives applied as a spray to tomato leaves subsequently exposed to tobacco hornworm larvae for 4 days.

Figure 1D is a graph showing the effect of the same xanthine derivatives on inhibiting cyclic AMP phosphodiesterase activity in homogenates of tobacco hornworm nerve cord.

Figure 2 is a graph showing the phosphodiesterase inhibiting activity of various xanthine derivatives in tobacco hornworm nerve cord.

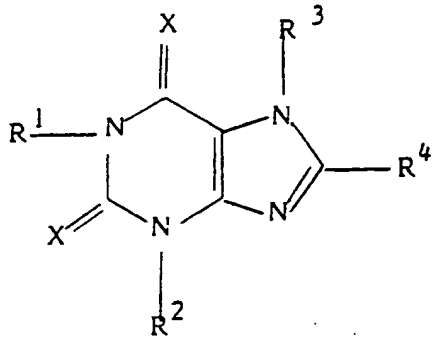
## BEST MODE OF CARRYING OUT THE INVENTION

By the terms "pest-controlling" or "pest-controlling activity," used throughout the specification and claims, are meant to include any pesticidal (killing) or pestistatic (inhibiting, maiming or generally interfering) activities of a composition against a given pest. Thus, these terms not only include killing, but also include such activities as those of chemisterilants which produce sterility in insects by preventing the production of ova or sperm, by causing death of sperm or ova, or by producing severe injury to the genetic material of sperm or ova, so that tha larvae that are produced do not develop into mature progeny.

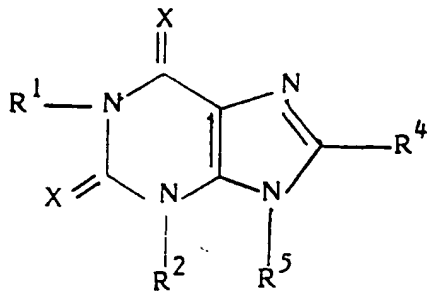
By the term "inhibiting the feeding" is meant to include both pesticidal activity wherein the pest is killed by the compound, as well as the situation wherein the feeding activity of the larvae is substantially affected and limited.

By the term "pest" is meant any phosphodiesterase-containing invertebrate. These pests include, but are not limited to, round worms (for example, hookworms, trichina, and ascaris); flat worms (for example, liver flukes and tapeworms); jointed worms (for example, leeches); molluscs (for example, parasitic snails); and arthropods (insects, spiders, centipedes, millipedes, crustaceans (for example, barnacles)). In particular, included among the arthropods are ticks, mites (both plant and animal), lepidoptera (butterflies and moths and their larvae), hemiptera (bugs), homoptera (aphids, scales), and coleoptera (beetles). Also included are spiders, anoplura (lice), diptera (flies and mosquitos), tricoptera, orthoptera (for example, roaches), odonta, thysanura (for example, silverfish), collembola (for example, fleas), dermaptera (earwigs), isoptera (termites), ephemerids (mayflies), plecoptera, malophaga (biting lice), thysanoptera, and siphonaptera (dictyoptera, psocoptera, and certain hymenoptera (for example, those whose larvae feed on leaves)).

By the term "xanthine derivative" or "methyl xanthine derivatives" are meant compounds having the general formula (I) or (II):



(I)



(II)

and their acid addition salts, wherein:

X is oxygen or sulfur;

$R^1$, $R^2$, $R^3$, $R^4$ and $R^5$ are selected from hydrogen; aliphatic and cycloaliphatic hydrocarbons having 1-8 carbon atoms; aliphatic and cycloaliphatic hydrocarbons substituted with 1-3 halogen atoms, lower alkyl ($C_1$-$C_4$), or hydroxy; alkoxy having 1-6 carbon atoms; aromatic; halo, hydroxy, or lower alkyl-substituted aromatic; phenoxy; substituted phenoxy; and the like, and further wherein at least one of $R^1$, $R^2$, $R^3$ or $R^5$ is other than hydrogen.

Suitable aliphatic hydrocarbon compounds include alkyl, alkenyl, alkynyl and the like.

Among the alkyl hydrocarbons are included methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, tert-pentyl, hexyl, heptyl, octyl, and the like.

Suitable alkenyl hydrocarbons are those having 2-8 carbon atoms and may include vinyl, allyl, isopropenyl, 1-propenyl, 2-butenyl, 3-pentenyl, 2-, 3-, or 4-hexenyl, and the like.

Suitable alkynyl hydrocarbons are those having 2-8 carbon atoms and may include ethynyl, 2-propynyl,

2-butynyl, 3-pentynyl, 3-hexynyl, 2-, 3-, or 4-heptynyl, and the like.

Suitable cylcoaliphatic groups include those having 3-8 carbon atoms, for example, cyclopentyl, cycloheptanyl, cyclohexanyl, cyclopentenyl, cyclohexynyl, and the like, as well as lower alkyl, halo or hydroxy substituted alkoxy groups.

Suitable alkoxy groups include methoxy, ethoxy, butoxy, pentoxy, and the like.

Suitable aromatic groups include phenyl or naphthyl. Among the substituted aromatic groups are phenyl substituted in the ortho, meta, and/or para positions with lower alkyl groups having 1-4 carbon atoms, halogens, and hydroxy.

Where the compounds are intended as pesticides, the fluoride salts are generally excluded; where the compounds are intended as pestistats, caffeine is excluded.

The preparation and/or source for the compounds are well known, see Wells, J. N., et al., Journal of Medicinal Chemistry, 24: 954-958 (1981); Kramer, G.I., et al., Biochemistry, Volume 16, Number 15, pages 3316-3321 (1977); Bruns, R. F., Biochemical Pharmacology, Volume 30, pages 325-333 (1981); and Garst, J.E., et al., Journal of Medicinal Chemistry, Volume 19, Number 4, pages 499-503 (1976).

Among the above-described xanthine derivatives, certain compounds have been shown to be especially effective. Thus, bulky substitution in the 3-position ($R^2$) increases activity substantially, with 3-isobutyl xanthine derivatives demonstrating superior effectiveness among the preferred compounds. Further,

substitution of small to medium (methyl, ethyl, propyl, i-propyl) groups in the 1-position ($R^1$) increases activity. Small to medium group substitution on the 7-position ($R^3$) also will enhance activity, as will certain small to medium group in the 8-position ($R^4$). However, chloro or bulky substituent in the 8-position ($R^4$) decreases activity as do certain substitutions in the 9-position ($R^5$).

The preferred compounds of the present invention are further defined as those compounds having a $V_{max}$ of more than 50% inhibition of feeding and an $EC_{50}$ of less than a 3% (gm/100 ml) concentration of spray. $V_{max}$ is expressed as the percent inhibition of feeding at the highest dose used (usually a 3% spray solution). $EC_{50}$ is the spray concentration (as calculated from dose-response curves) required to cause 50% inhibition of feeding. Inhibition of feeding is determined at a time when untreated leaves show 20% of leaf area remaining. Calculation is then made by determining the percent leaf area remaining on leaves sprayed with drugs minus 20 divided by 80 (the maximal inhibition of feeding possible). The inhibition of feeding determination will be described in detail below. Basically, leaves are eaten by first-instar Manduca sexta which are placed at 6 per leaf.

In addition to Manduca sexta, other examples of insect species demonstrated to be affected by xanthine derivatives are Tenebrio (mealworn) larvae ($EC_{50}$ 0.1-0.3%); Vanessa cardui (painted lady butterfly) larvae ($EC_{50}$ 0.1-0.3%); Oncopeltus fasciatus (milkweed bug) nymph ($EC_{50}$ 0.3%); and, in solution, 1-methyl-3-isobutyl xanthine (IBMX) killed Culex (mosquito)

larvae ($EC_{50}$ 0.007%). Tribolium confusum and Tribolium castaneum (flower beetle) adults were unaffected by IBMX doses up to 3%. However, in chronic tests, IBMX ($EC_{50}$ 0.2%) inhibited reproduction of these two species.

As mentioned above, in vertebrate tissues, methylxanthines are known to inhibit phosphodiesterase (PDE), enzymes which hydrolyze cAMP. Rall, T. W., Pharmacological Bases of Therapeutics, A. G. Gillman, L. Goodman, A. Gillman, Editors (MacMillan, New York, 1980), p. 592; Sutherland, E. W., et al., Journal of Biological Chemistry, 232: 1077 (1958); and Butcher, R. W., et al., Journal of Biological Chemistry, 237: 1244 (1962). It was thus investigated as to whether xanthine derivatives could inhibit Manduca nerve cord PDE activity and, if so, whether the degree of such inhibition was related to observed pestistatic and pesticidal activity. The methodology for determining PDE inhibition is described below in Examples 8-11. These examples and Figure 1D demonstrate the dose-dependent inhibition of nerve cord PDE activity by various xanthine derivatives whose inhibitory effects on leaf consumption are shown in Examples 4-7 and Figure 1C.

The similarity of the graphs in Figures 1C and 1D demonstrates a strong correlation between PDE inhibition and pesticidal and pestistatic activity. This correlation is further evaluated in Examples 15 through 42 below. Based on the work to date, the most preferred compounds according to the present invention are those xanthine derivatives according to structural formulas (I) and (II) which also demonstrate a $K_i$ of

0.1 mM or less, wherein $K_i$ is defined as the concentration of xanthine derivative necessary to produce a 50% inhibition of enzyme activity for hornworm nerve cord PDE. Inhibition of phosphodiesterase activity for hornworm nerve cord for the purposes of determining $K_i$ within the meaning of this invention is determined in accordance with the methodology set out in Examples 8-11.

The pest-controlling agents of the present invention may be formulated as dusts, water dispersions, emulsions and solutions. They may comprise accessory agents such as dust carriers, solvents, emulsifiers, wetting and dispersing agents, stickers, deodorants, and masking agents (see, for example, Encyclopedia of Chemical Technology, Volume 13, pages 416 et seq.).

Dusts generally will contain low concentrations, 0.1-20%, of the compounds, although ground preparations may be used and diluted. Carriers commonly include organic flowers, sulfur, silicon oxides, lime, gypsum, talc, pyrophyllite, bentonite, kaolins, attapulgite, and volcanic ash. Selection of the carrier may be made on the basis of compatibility with the desired pest control composition (including pH, moisture content, and stability), particle size, abrasiveness, absorbability, density, wettability and cost. The agent of the invention, alone or in combination, and eluent is made by a variety of simple operations such as milling, solvent impregnations, fusing and grinding. Particle sizes usually range from 0.5-4.0 microns in diameter.

Wettable powders may be prepared by blending the agents of the invention in high concentrations, usually from 15-95%, with a dust carrier such as bentonite

which wets and suspends properly in water. Twenty-two percent of a surface-active agent is usually added to improve the wetting and suspendability of the powder.

The pest-controlling agents may also be used in granules, which are pelleted mixtures of the agents, usually at 2.5-10%, and a dust carrier, for example, adsorptive clay, bentonite or diatomaceous earth, and commonly within particle sizes of 250-590 microns. Granules may be prepared by impregnations of the carrier with a solution or slurry of the agents and may be used principally for mosquito larvae treatment or soil applications.

The agent may also be applied in the form of an emulsion, which comprises a solution of the agents in water-immiscible organic solvents, commonly at 15-50%, with a few percent of surface active agent to promote emulsification, wetting, and spreading. The choice of solvent is predicated upon solubility, safety to plants and animals, volatility, flammability, compatibility, odor and cost. The most commonly used solvents are kerosene, xylenes, and related petroleum fractions, methylisobutylketone, and amyl acetate. Water emulsion sprays from such emulsive concentrates may be used for plant protection and for household insect control.

The agents may also be mixed with baits, usually comprising 1-5% of agents with a carrier especially attractive to insects. Carriers include sugar for houseflies, protein hydrolysate for fruit flies, bran for grasshoppers, and honey, chocolate, or peanut butter for ants.

The agents may be included in slow release formulations which incorporate non-persistent compounds,

insect growth regulators and sex pheromones in a variety of granular microencapsulated and hollow fiber preparations.

The pest-controlling agents of the present invention may be applied depending on the properties of the particular pest-controlling compound, the habits of the pest to be controlled, and the site of the application to be made. It may be applied by spraying, dusting or fumigation.

Doses of the weight of the ingredients may typically vary between 0.001 and 100 pounds/acre, preferably between 0.001-5 pounds/acre.

Sprays are the most common means of application and generally will involve the use of water as the principal carrier, although volatile oils may also be used. The pest-controlling agents of the invention may be used in dilute sprays (for example, 0.001-10%) or in concentrate sprays in which the composition is contained at 10-98%, and the amount of carrier to be applied is quite reduced. The use of concentrate and ultra-low volume sprays will allow the use of atomizing nozzles producing droplets of 30-80 microns in diameter. Spraying may be carried out by airplane or helicopter.

Aerosols may also be used to apply the pest-controlling agents. These are particularly preferred as space sprays for application to enclosures, particularly against flying insects. Aerosols are applied by atomizing amounts of liquified gas dispersion or bomb, but can be generated on a larger scale by rotary atomizers or twin-fluid atomizers.

A simple means of pest-controlling agent dispersal is by dusting. The pest-controlling agent is applied

by introducing a finely divided carrier with particles typically of 0.5-3 microns in diameter into a moving air stream.

Having now generally described the invention, the same will become better understood by reference to certain specific examples which are included herein for purposes of illustration only and are not intended to be limiting unless otherwise specified.

**Example 1**

Various concentrations of finely powdered tea leaves or powdered coffee beans were mixed in artificial media which was then plated out in small petri dishes and allowed to harden. At concentrations from 0.3-10% (wt/wt) for coffee and from 0.1-3% for tea, larvae of Manduca sexta (tobacco hornworm) housed in these dishes showed a dose-dependent inhibition of feeding associated with hyperactivity, tremors and stunted growth. At concentrations greater than 10% (for coffee) or 3% (for tea), larvae were killed within 24 hours.

**Example 2**

The larvae of Manduca sexta were fed on either artificial or natural food. When added to artificial media, caffeine (the major methylxanthine found in tea and coffee) exerted behavioral effects that were qualitatively similar to those of the tea and coffee described above. In addition, as Figure 1A shows, the concentration of purified caffeine required for 50% inhibition of weight gain was nearly identical to the endogenous caffeine content of the coffee-media mixture which caused 50% inhibition of weight gain.

Further, the dried tea leaves, which contain 2-3 times the caffeine content of dried coffee beans, were about 2-3 times as effective as coffee beans in inhibiting weight gain. Further, the concentrations of caffeine which are found naturally in undried tea leaves (0.68-2.1%) or coffee beans (0.8-1.8%) were sufficient to kill most Manduca larvae. Thus, caffeine functions as an endogenous insecticide.

**Example 3**

Various xanthine derivatives were tested on natural feeding substrates, such as tomato leaves, the xanthine derivatives being those compounds wherein at least one of $R^1$, $R^2$, $R^3$, and $R^5$ are other than hydrogen. The compounds, applied as a spray, exerted pestistatic and pesticidal effects which resulted in leaf protection. Figure 1B shows a typical result for caffeine.

**Examples 4-7**

Figure 1C (which quantitates the amount of leaf remaining) summarizes the dose-response curves for caffeine (Example 4), theophylline (Example 5), and the synthetic compound, 1-methyl-3-isobutylxanthine (IBMX) (Example 6). In Example 3 above and each of Examples 4-6, isolated hydrated tomatoe leaves were pre-sprayed with the compound(s) or vehicle (usually MeOH) at the concentration shown, allowed to dry and placed in closed plexiglass containers. A group of six, three-day old tobacco hornworm larvae (initially reared on artificial media) were then placed on each leaf, and the amount of leaf remaining was measured at

the end of four days. Values shown are the mean (± SEM) of three separate experiments. Figure 1C also shows the relatively weak effects of 8-phenyltheophylline (Example 7), a known adenosine receptor blocker (Daly, J. W., Journal of Medicinal Chemistry, 25: 197 (1982)).

**Examples 8-11**

Nerve cord was dissected from 40-60 mm long M. sexta larvae, cleaned, and homogenized (2 mg/ml) in 6 Mm Tris-maleate, pH 7.4. PDE activity was measured (4 min. incubation at 30°C) in an assay system (0.1 ml) containing 80 mM Tris-maleate, pH 7.4; 6 mM Mg-$SO_4$; $10^{-7}$ M $^3$H-cyclic AMP; and tissue homogenate (0.02 ml). Nerve cord was evaluated in the presence and the absence of the xanthine derivative. For purposes of the evaluation, the rate of formation of $^3$H-5' AMP was measured using the technique described in Filburn, C.R., Annals of Biochemistry, 52: 505 (1973). Under these conditions, enzyme activity was linear with respect to time and enzyme concentration. The values shown in Figure 1D are the mean (± SEM) of three separate experiments. As may be seen, the patterns of activity in the two graphs are quite similar.

**Example 12**

To determine if the dosage of xanthine derivatives described in experiments 4, 7 and 8-11 and ingested by the larvae (causing pestistatic and pesticidal activity in vivo) were actually absorbed by the animals and were sufficient to inhibit PDE in vitro, additional experiments were carried out in order to estimate

tissue levels of xanthine derivative following three days of feeding on various doses of the derivative. Groups of six larvae were placed on leaves treated with vehicle or theophylline spray. After three days, leaf area was recorded and larvae (alive or dead) were rinsed to remove any compound adhering to their cuticle, homogenized whole, centrifuged, and the cell-free supernatant assayed for theophylline content by immunoenzymatic assay (Emit-AAD theophylline assay (Syva Company, Palo Alto, California)). This particular assay shows little cross-reactivity with theophylline metabolites. From mammalian studies, it is known that theophylline penetrates freely into all body compartments (Rall, T. W., supra.). Larvae feeding on leaves treated with a 1% spray (an amount causing about 50% inhibition of leaf consumption) were found to contain an internal theophylline concentration of 4.1 $\pm$ 1.1 mM (mean $\pm$ deviation for two groups of six pooled animals). This concentration was sufficient to cause more than an 80% inhibition of hornworm nerve cord PDE activity in vitro. This observation tends to rule out the hypothesis wherein adenosine receptors are involved as a mechanism for the antifeeding effects of the xanthine derivatives, since, in vertebrates, xanthine derivatives such as theophylline are competitive adenosine receptor antagonists, but exert such antagonism at much lower concentrations, typically 1-25 micromoles. See Bruns, R., et al., Proceedings of the National Academy of Sciences, USA, 77: 5547 (1980); Williams, M., et al., Proceedings of the National Academy of Sciences, USA, 77: 6892 (1980).

**Example 13**

Xanthine derivatives have been reported to have calcium mobilizing effects (Links, J. R., et al., Circulation Research, 30: 367 (1972)). Xanthine derivatives are known to mobilize calcium from sarcoplasmic reticulum, an effect which is blocked by diltiazem or procaine. IBMX was evaluated with regard to antifeeding effects in the presence of both diltiazem and procaine, neither reversing the observed antifeeding effects.

**Example 14**

Xanthine derivatives have also been reported to affect calcium movement across the plasma membrane (Links, J. R., et al., supra; Saeki, K., et al., Life Sciences, 32: 2973 (1983)). The pestistatic and pesticidal effects of IBMX were evaluated in the presence of D600, verapamil, and nimodipine, compounds which are known to block plasma membrane calcium channels. The pestistatic and pesticidal effects of IBMX appeared unaffected by these compounds.

**Discussion**

Whereas caffeine has been reported to be 10-fold weaker than theophylline as an adenosine antagonist (Bruns, R., et al., supra), as demonstrated by the above Examples, caffeine was somewhat more potent than theophylline in preventing leaf eating and about equally potent as a PDE inhibitor. See Figures 1C and 1D. Also, whereas IBMX and theophylline are roughly equally potent in blocking adenosine receptors (Bruns, R., et al., supra) IBMX was about 10-fold more potent

both in disruption of feeding and in PDE inhibition. See Figure 1D. Furthermore, the very potent adenosine antagonist, 8-phenyltheophylline ($K_i$ for adenosine receptor (0.12-1.0 micromoles) (Daly, J. W., Journal of Medicinal Chemistry, 25: 197 (1982); Bruns, R., et al., supra) exerted little antifeeding effect and was a very weak PDE inhibitor (see Figures 1C and 1D). Additionally, the non-xanthine, papavarine, was a potent inhibitor both of insect PDE ($K_i$ = 40 micromoles) and of the ability of Manduca to feed ($EC_{50}$ = 0.1% spray). Unlike xanthine derivatives, papavarine is an inhibitor of adenosine uptake, and it potentiates, rather than blocks physiological effects on adenosine receptors (Huang, M., et al., Life Sciences, 14: 489 (1974)). Taken together, these data are more consistent with a mechanism of action related to PDE inhibition than to adenosine blockade.

Cumulatively, these data suggest that pestistatic and pesticidal effects of the xanthine derivatives are mediated through an alteration of tissue cyclic AMP levels, most likely secondarily to an inhibition of phosphodiesterase. Thus, the naturally occurring xanthine derivatives function as endogenous pest-controlling agents.

## Examples 15-41

Twenty-seven compounds conforming to the general formula (I) or (II) above were prepared or obtained and evaluated with regard to pesticidal and pestistatic activity. The results of the evaluation are reported in Table 1 below. In Table 1 below, $EC_{50}$ and $V_{max}$ are as described above, with active compounds

being those compounds with a $V_{max}$ of more than 50% inhibition of feeding and an $EC_{50}$ of less than 3% (gm/100 ml) concentration of spray. As may be seen from Table 1, Examples 15-27 are active compounds within the above meaning, with Examples 28-40 being inactive compounds. Example 41 is weakly active. Of the thirteen active compounds, eight are more active than caffeine (1,3,7-trimethylxanthine), Examples 16-21, 24, and 26.

**Table 1**

**STRUCTURAL-ACTIVITY RELATIONSHIPS OF XANTHINES WITH PESTICIDAL ACTIVITY**

| Ex. | Compound | $EC_{50}$ | $V_{max}$ |
|---|---|---|---|
| Active Compounds | | | |
| 15 | 1,3-dimethylxanthine (theophylline) | 1.5 | 94 |
| 16 | 1,3-diethylxanthine | 0.33 | 98 |
| 17 | 1,3-dipropyl-xanthine | 0.035 | 95 |
| 18 | 1,3-diallyl-xanthine | 0.35 | 99 |
| 19 | 1,3-dibenzyl-xanthine | 0.45 | 70 |
| 20 | 1-methyl,3-isobutyl-xanthine | 0.3 | 95 |
| 21 | 1-isoamyl,3-isobutyl-xanthine | 0.2 | >52 |
| 22 | 1-phenethyl,3-ethyl-xanthine | 3.0 | 50 |
| 23 | 1,3,7-trimethyl-xanthine (caffeine) | 0.6 | 96 |
| 24 | 1,3-dimethyl,7-(2-chlorethyl)-xanthine | 0.3 | 98 |
| 25 | 1,3-dimethyl,7-(beta-hydroxypropyl-xanthine). | 1.5 | 95 |
| 26 | 1,3,7-trimethyl,8-methoxy-xanthine | 0.5 | 86 |
| 27 | 3,7-dimethyl-xanthine (theobromine) | 1.0 | 87 |
| Inactive Compounds | | | |
| 28 | xanthine | >3 | 0 |
| 29 | 1-methyl-xanthine | >3 | 21 |
| 30 | 3-methyl-xanthine | >3 | 8 |
| 31 | 7-methyl-xanthine | >3 | 29 |
| 32 | 8-methyl-xanthine | >3 | 35 |
| 33 | 9-methyl-xanthine | >3 | 10 |
| 34 | 1,7-dimethyl-xanthine | >3 | 30 |
| 35 | 1,7-dimethyl-uric acid | >3 | 30 |
| 36 | 1,3,7-trimethyl-uric acid | >3 | 40 |
| 37 | 1,3-dimethyl-7-acetyl-xanthine | >3 | 18 |
| 38 | 1,3-dimethyl-8-phenyl-xanthine | >3 | 38 |
| 39 | 1,3-dipropyl-8-phenyl-xanthine | >1 | 0 |
| 40 | 1,3,7-trimethyl-8-chloro-xanthine | >3 | 40 |
| Weakly Active | | | |
| 41 | 1,3,9-trimethyl-xanthine | >3 | 50 |

**Example 42**

Fifteen xanthine derivatives, and xanthine itself, were evaluated according to their ability to inhibit phosphodiesterase activity in hornworm nerve cord using the methodology set out in Examples 8-11 above. The sixteen compounds and the identifying key for Figure 2 appear in Table 2 below. As may be seen from Figure 2, compounds 1-5 have a $K_i$ ($K_i$, as defined above, being the concentration in mM necessary to cause a 50% inhibition in PDE activity) of 0.1 or less. These same five compounds have a $V_{max}$ of at least 95 and an $EC_{50}$ of 0.33 or less.

**Table 2**

KEY FOR GRAPH OF FIGURE 2

Inactive Compounds

A. 1,3-dimethyl-7-acetyl-xanthine
B. 1-methyl-xanthine
C. 8-methyl-xanthine
D. xanthine
E. 7-methyl-xanthine
F. 3-methyl-xanthine
G. 1,3-dimethyl-8-chloro-xanthine
H. 1,3-dimethyl-8-phenyl-xanthine

Active Compounds

1. 1,3-dipropyl-xanthine
2. 1-methyl,3-isobutyl-xanthine
3. 1,3-diallyl-xanthine
4. 1,3-diethyl-xanthine
5. 1,3-dimethyl-7-(2-chlorethyl)-xanthine
6. 1,3-dimethyl-xanthine (theophylline)
7. 1,3,7-trimethyl-xanthine (caffeine)
8. 1,3-dimethyl-7-(beta-hydroxypropyl)-xanthine

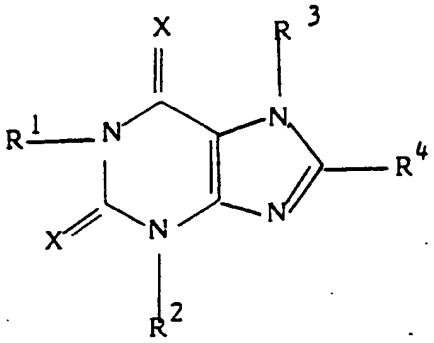
This strong correlation between in vitro PDE inhibition and pesticidal activity allows one to accurately predict the pesticidal activity of xanthine

derivatives based on PDE inhibition in tobacco hornworm nerve cord.

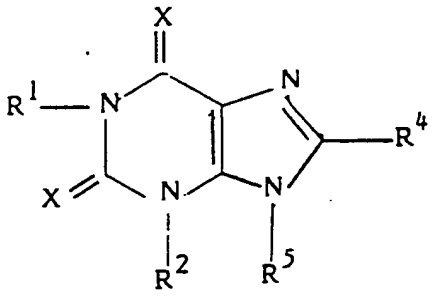
Having now fully described this invention, it will be understood by those of skill in the art that the same may be performed within a wide and equivalent range of compositions, parameters, structures, modes of application, pests, formulations, and ranges without affecting the scope of the invention or any embodiment thereof.

**WHAT IS CLAIMED AND DESIRED TO BE COVERED BY LETTERS PATENT IS:**

1. A method of pest control comprising bringing into contact with said pest a pest-controlling amount of a xanthine derivative having the general formula:



or



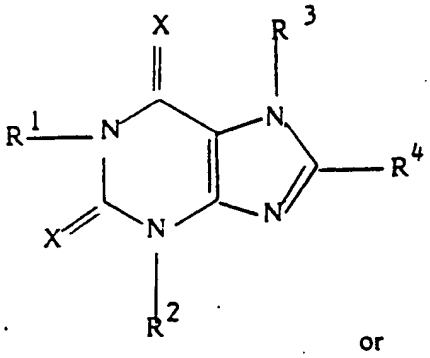
and the acid addition salts thereof, wherein

X is oxygen or sulfur; and

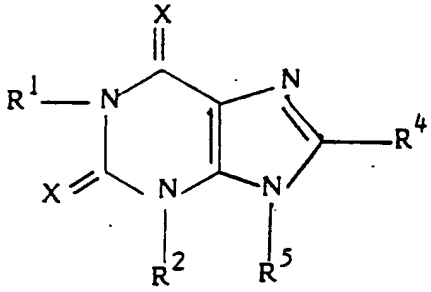
$R^1$, $R^2$, $R^3$, $R^4$ and $R^5$ are selected from hydrogen; aliphatic and cycloaliphatic hydrocarbons having 1-8 carbon atoms; aliphatic and cycloaliphatic hydrocarbons substituted with 1-3 halogen atoms, lower ($C_1$-$C_4$) alkyl, or hydroxy; alkoxy having 1-6 carbon atoms; aromatic; halo, hydroxy, or lower ($C_1$-$C_4$) alkyl-substituted aromatic; phenoxy; or substituted phenoxy;

with the proviso that $R^1$, $R^2$, $R^3$ and $R^5$ are not each methyl simultaneously and at least one of $R^1$, $R^2$, $R^3$, and $R^5$ is other than hydrogen.

2. A method of pest controlling comprising bringing into contact with said pest a pest-controlling amount of a xanthine derivative having the general formula:



or



and the acid addition salts thereof, wherein

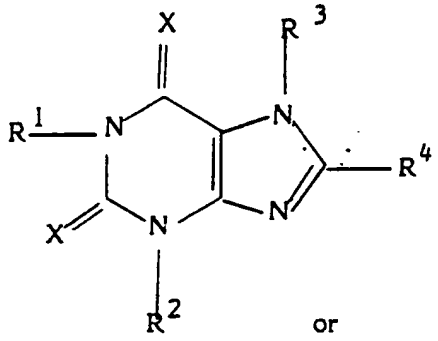
X is oxygen or sulfur; and

$R^1$, $R^2$, $R^3$, $R^4$ and $R^5$ are selected from hydrogen; aliphatic and cycloaliphatic hydrocarbons having 1-8 carbon atoms; aliphatic and cycloaliphatic hydrocarbons substituted with 1-3 halogen atoms, lower ($C_1$-$C_4$) alkyl, or hydroxy; alkoxy having 1-6 carbon atoms; aromatic; halo, hydroxy, or lower ($C_1$-$C_4$) alkyl-substituted aromatic; phenoxy; or substituted phenoxy;

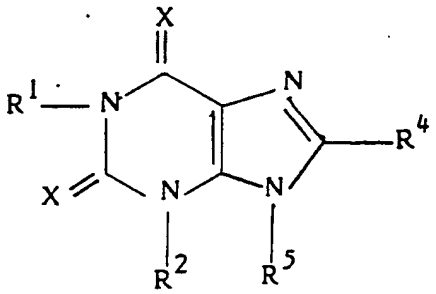
with the proviso that $R^1$, $R^2$, $R^3$, and $R^5$ are not each methyl simultaneously, at least one of $R^1$, $R^2$, $R^3$, and $R^5$ is other than hydrogen and

with the further proviso that, in a system comprising a compound as above, the compound has a $V_{max}$ of more than 50 and an $EC_{50}$ of no more than 3, where $V_{max}$ is expressed as the percent inhibition of feeding at a 3% (gm/100 ml) concentration of spray and $EC_{50}$ is defined as the spray concentration (gm/100 ml) required to cause a 50% inhibition of feeding.

3. A method of inhibiting the feeding of a pest comprising bringing into contact with said pest a feeding-inhibiting amount of a xanthine derivative having the general formula:



or



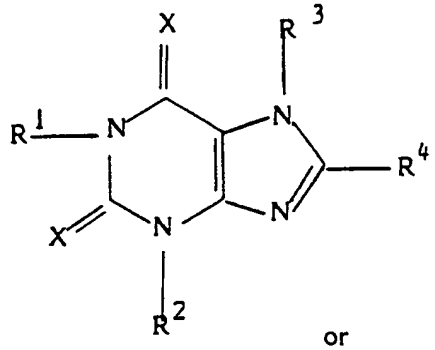
and the non-hydrogen fluoride acid addition salts thereof, wherein

X is oxygen or sulfur; and

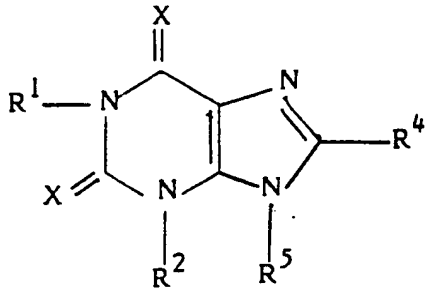
$R^1$, $R^2$, $R^3$, $R^4$ and $R^5$ are selected from hydrogen; aliphatic and cycloaliphatic hydrocarbons having 1-8 carbon atoms; aliphatic and cycloaliphatic hydrocarbons substituted with 1-3 halogen atoms, lower ($C_1$-$C_4$) alkyl, or hydroxy; alkoxy having 1-6 carbon atoms; aromatic; halo, hydroxy, or lower ($C_1$-$C_4$) alkyl-substituted aromatic; phenoxy; or substituted phenoxy;

and with the proviso that at least one of $R^1$, $R^2$, $R^3$ and $R_5$ is other than hydrogen.

4. A method of inhibiting the feeding of a pest comprising bringing into contact with said pest a feed-inhibiting amount of a xanthine derivative having the general formula:



or



and the non-hydrogen fluoride acid addition salts thereof, wherein

X is oxygen or sulfur; and

$R^1$, $R^2$, $R^3$, $R^4$ and $R^5$ are selected from hydrogen; aliphatic and cycloaliphatic hydrocarbons having 1-8 carbon atoms; aliphatic and cycloaliphatic hydrocarbons substituted with 1-3 halogen atoms, lower alkyl, or hydroxy; alkoxy having 1-6 carbon atoms; aromatic; halo, hydroxy, or lower alkyl-substituted aromatic; phenoxy; or substituted phenoxy;

with the proviso that $R^1$, $R^2$, $R^3$, and $R^5$ are not each methyl simultaneously, and at least one of $R^1$, $R^2$, $R^3$, and $R^5$ is other than hydrogen, and

with the further proviso that, in a system comprising a compound as above, said compound has a $V_{max}$ of more than 50 and an $EC_{50}$ of no more than 3, where $V_{max}$ is expressed as the percent inhibition of feeding at a 3% (gm/100 ml) concentration of spray and $EC_{50}$ is defined as the spray concentration (gm/100 ml) required to cause a 50% inhibition of feeding.

5. The method of Claim 1 wherein the xanthine derivative is selected from the group consisting of 1,3-dimethyl-xanthine; 1,3-diethyl-xanthine; 1,3-dipropyl-xanthine; 1,3-diallyl-xanthine; 1,3-dibenzyl-xanthine; 1-methyl,3-isobutyl-xanthine; 1-isoamyl-3-isobutyl-xanthine; 1-phenethyl-3-ethyl-xanthine; 1,3-dimethyl-7-(2-chlorethyl)-xanthine; 1,3-dimethyl-7-(beta-hydroxypropyl)-xanthine; 1,3,7-trimethyl-8-methoxy-xanthine; and 3,7-dimethyl-xanthine.

6. The method of Claim 2 wherein said xanthine derivative is selected from the group consisting of 1,3-dimethyl-xanthine, 1,3-diethyl-xanthine; 1,3-dipropyl-xanthine; 1,3-diallyl-xanthine; 1,3-dibenzyl-xanthine; 1-methyl-3-isobutyl-xanthine; 1-isoamyl-3-isobutyl-xanthine; 1-phenethyl-3-ethyl-xanthine; 1,3-dimethyl-7-(2-chlorethyl)-xanthine; 1,3-dimethyl-7-(beta-hydroxypropyl)-xanthine; 1,3,7-trimethyl-8-methoxy-xanthine; and 3,7-dimethyl-xanthine.

7. The method of Claim 3 wherein said xanthine derivative is selected from the group consisting of 1,3-dimethyl-xanthine; 1,3-diethyl-xanthine; 1,3-dipropyl-xanthine; 1,3-diallyl-xanthine; 1,3-dibenzyl-

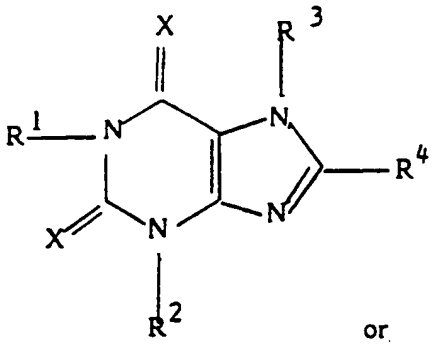
xanthine; 1-methyl-3-isobutyl-xanthine; 1-isoamyl-3-isobutyl-xanthine; 1-phenethyl-3-ethyl-xanthine; 1,3-dimethyl-7-(2-chlorethyl)-xanthine; 1,3-dimethyl-7-(beta-hydroxypropyl)-xanthine; 1,3,7-trimethyl-8-methoxy-xanthine; 3,7-dimethyl-xanthine; and 1,3,7-trimethyl-xanthine.

8. The method of Claim 4 wherein said xanthine derivative is selected from the group consisting of 1,3-dimethyl-xanthine; 1,3-diethyl-xanthine; 1,3-dipropyl-xanthine; 1,3-diallyl-xanthine; 1,3-dibenzyl-xanthine; 1-methyl-3-isobutyl-xanthine; 1-isoamyl-3-isobutyl-xanthine; 1-phenethyl-3-ethyl-xanthine; 1,3-dimethyl-7-(2-chlorethyl)-xanthine; 1,3-dimethyl-7-(beta-hydroxypropyl)-xanthine; 1,3,7-trimethyl-8-methoxy-xanthine; 3,7-dimethyl-xanthine; and 1,3,7-trimethyl-xanthine.

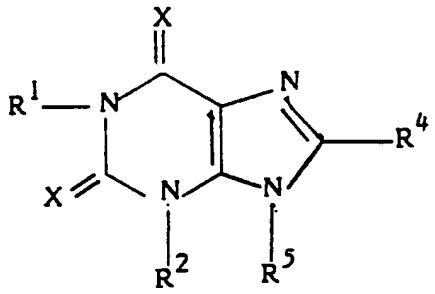
9. The method of Claim 1 wherein said xanthine derivative has a $K_i$ of not greater than 0.1, where $K_i$ is defined as the concentration in mM of said xanthine derivative required to produce a 50% inhibition of enzyme activity for hornworm nerve cord phosphodiesterase.

10. The method of Claim 3 wherein said xanthine derivative has a $K_i$ of not greater than 0.1, where $K_i$ is defined as the concentration in mM of said xanthine derivative required to produce a 50% inhibition of enzyme activity for hornworm nerve cord phosphodiesterase.

11. A pest-controlling composition in the form of a dust comprising a pest-controlling amount of an agent selected from xanthine derivatives having the general formula:



or



and the acid addition salts thereof, wherein

X is oxygen or sulfur; and

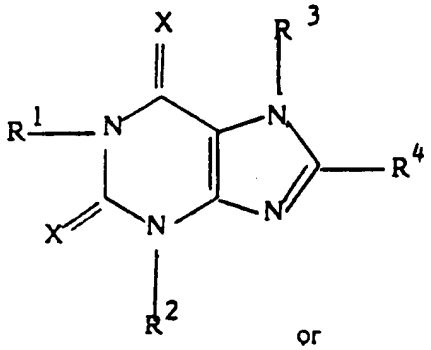
$R^1$, $R^2$, $R^3$, $R^4$ and $R^5$ are selected from hydrogen; aliphatic and cycloaliphatic hydrocarbons having 1-8 carbon atoms; aliphatic and cycloaliphatic hydrocarbons substituted with 1-3 halogen atoms, lower ($C_1$-$C_4$) alkyl, or hydroxy; alkoxy having 1-6 carbon atoms; aromatic; halo, hydroxy, or lower ($C_1$-$C_4$) alkyl-substituted aromatic; phenoxy; or substituted phenoxy;

with the proviso that $R^1$, $R^2$, $R^3$ and $R^5$ are not each methyl simultaneously and at least one of $R^1$, $R^2$, $R^3$, and $R^5$ is other than hydrogen, together with a pesticidally inert dust carrier.

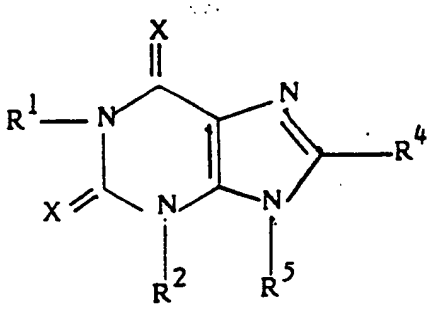
12. The composition of Claim 11 wherein said carrier is selected from the group consisting of

organic flour, sulfur, silicon oxides, lime, gypsum, talc, pyrophyllite, bentonite, kaolin, attapulgite, and volcanic ash.

13. A pest-controlling composition in the form of a granule or pellet comprising a pest-controlling amount of an agent selected from a xanthine derivative having the general formula:



or



and the acid addition salts thereof, wherein

X is oxygen or sulfur; and

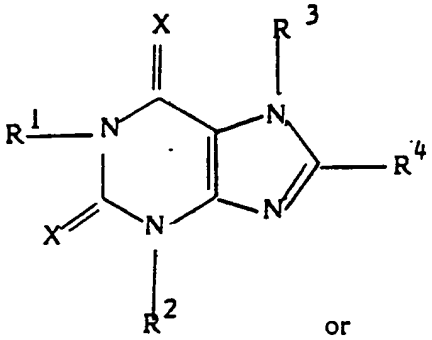
$R^1$, $R^2$, $R^3$, $R^4$ and $R^5$ are selected from hydrogen; aliphatic and cycloaliphatic hydrocarbons having 1-8 carbon atoms; aliphatic and cycloaliphatic hydrocarbons substituted with 1-3 halogen atoms, lower ($C_1$-$C_4$) alkyl, or hydroxy; alkoxy having 1-6 carbon atoms; aromatic; halo, hydroxy, or lower ($C_1$-$C_4$) alkyl-substituted aromatic; phenoxy; or substituted phenoxy;

with the proviso that $R^1$, $R^2$, $R^3$ and $R^5$ are not each methyl simultaneously and at least one of $R^1$, $R^2$,

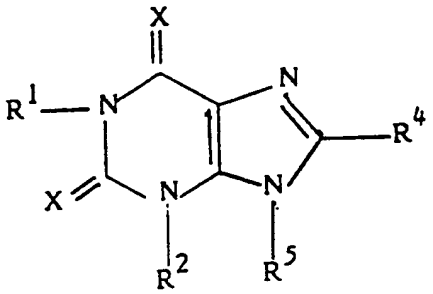
$R^3$, and $R^5$ is other than hydrogen, together with a granule- or pellet-forming inert carrier.

14. The composition of Claim 13 wherein said granule- or pellet-forming carrier is selected from the group consisting of organic flour, sulfur, silicon oxides, lime, gypsum, talc, pyrophyllite, bentonite, kaolin, attapulgite and volcanic ash.

15. A pest-controlling composition in the form of an aerosol which comprises a pest-controlling amount of an agent selected from a xanthine derivative having the general formula:



or



and the acid addition salts thereof, wherein

X is oxygen or sulfur; and

$R^1$, $R^2$, $R^3$, $R^4$ and $R^5$ are selected from hydrogen; aliphatic and cycloaliphatic hydrocarbons having 1-8 carbon atoms; aliphatic and cycloaliphatic hydrocarbons substituted with 1-3 halogen atoms, lower ($C_1$-$C_4$)

alkyl, or hydroxy; alkoxy having 1-6 carbon atoms; aromatic; halo, hydroxy, or lower ($C_1$-$C_4$) alkyl-substituted aromatic; phenoxy; or substituted phenoxy;

with the proviso that $R^1$, $R^2$, $R^3$ and $R^5$ are not each methyl simultaneously and at least one of $R^1$, $R^2$, $R^3$, and $R^5$ is other than hydrogen, together with an atomizing amount of a liquified gas.

# INTERNATIONAL SEARCH REPORT

International Application No PCT/US85/01708

## I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int. Cl. 4 --A61L 9/04; A01N 43/90

## II. FIELDS SEARCHED

Minimum Documentation Searched [4]

| Classification System | Classification Symbols |
|---|---|
| U.S. | 424/45; 514/263, 265 |

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

LEXPAT-LEXIS 1975-1985--XANTHINE OR CAFFEIN! OR THEOPHYLLINE AND PEST! OR INSECT! CAS ON LINE 1965-1985 --XANTHINE OR CAFFEIN! OR THEOPHYLLINE AND PEST! OR INSECT!

## III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

| Category * | Citation of Document, [16] with indication, where appropriate, of the relevant passages [17] | Relevant to Claim No. [18] |
|---|---|---|
| X | N, King, Chemicals Evaluated as Insecticides and Repellents, pp. 1-21, 100-101 (1954) | 1-4; 7-8 |
| X | U.S., A, 3,663,692 (KARE), 16 May 1972 (16.5.72) | 1-4;7-8; 11-15 |
| A | U.S., A, 2,362,614 (CALVA), 14 November 1944 (14.11.44) | all |
| A | U.S., A, 1,653,710 (KITCHIN), 27 December 1927 (27.12.27) | all |
| X | N, Rojakovick et al, Pesticide Biochemistry and Physiology, 6, pp. 10-19 (1976) | 2,4,8 |

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

## IV. CERTIFICATION

| Date of the Actual Completion of the International Search [2] | Date of Mailing of this International Search Report [2] |
|---|---|
| November 22, 1985 | 26 NOV 1985 |
| **International Searching Authority [1]** | **Signature of Authorized Officer [20]** |
| ISA/US | Linda Abraham |

Form PCT/ISA/210 (second sheet) (October 1981)

FURTHER INF RMATION CONTINUED FROM THE SECOND SHEET

| | | |
|---|---|---|
| X | N, Rizvi et al., Journal of Applied Entomology, 90, pp. 378-81 (1980) | 2,4,8 |
| X | N, Janzen et al., Phytochemistry, 16, pp. 223-227 (1977) | 2,4,8 |
| X | N, Targa et al., Brazil J. Genetics, 4, pp. 669-677 (1982) | 2,4,8 |
| X | N, Srinivasan et al., Toxicology Letters, 3, pp. 101-105 (1979) | 2,4,8 |

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [10]

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers ....., because they relate to subject matter [12] not required to be searched by this Authority, namely:

2. ☐ Claim numbers ....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [13], specifically:

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [11]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

| Category * | Citation of Document, [16] with indication, where appropriate, of the relevant passages [17] | Relevant to Claim No [18] |
|---|---|---|
| A | N, Rizvi et al., Indian Journal of Experimental Biology, 18, pp. 777-8 (1980) | all |
| A | N, Rizvi et al. Agricultural and Biological Chemistry, 45, pp. 1255-6 (1981) | all |
| A | N, Cadena-Gomez, Abstracts of the American Phytopathological Society, Caribbean Division, 73, pg. 121 (1983) | all |
| A | N, Moffett et al., Comp. Biochem. Physiol., vol. 750, pp. 305-310 (1983) | all |
| A | N, Clark, Ent. Exp. and Appl., Vol. 29, pp. 189-197 (1981) | all |
| A | N, McDaniel, Insect Physiol. vol. 20, pp. 245-252(1974) | all |
| A | N, Srinivasan et al., J. of Toxicology and Enivronmental Health, Vol. 2. pp. 569-576 (1977) | all |
| A | Fr., B, 2, 138, 186 (ARIES), 5 January 1973 (5.1.73) | all |
| A | N, Srinivasan et al., Toxicology Letters, Vol. 3, pp. 229-232 (1979) | all |